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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,850	02/20/2004	Stevan P. Tofovic	007278-04	1648
36234	7590	08/05/2005	EXAMINER	
THE MCCALLUM LAW FIRM, LLC 132 KOLAR COURT ERIE, CO 80516			HUI, SAN MING R	
			ART UNIT	PAPER NUMBER
			1617	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,850	TOFOVIC ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9/27/05</u> <u>7/14/04</u> | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 1-36 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-9, 11-13, 15-17, 19-21, 23-25, 27-29, 31-33, 35-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 2-hydroxyestradiol, 2-methoxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol, does not reasonably provide enablement for other estradiol metabolites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApl 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence of absence of working examples,

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- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art
- 7) the predictability of the art, and
- 8) the breadth of the claims.

Applicant fails to provide information allowing the skilled artisan to ascertain these compounds possessing the recited, and claimed, physiological activity without undue experimentation.

- 1) the quantity of experimentation necessary,

The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "estradiol metabolites", necessitating an exhaustive search for all embodiments, regardless their chemical formula, or structure, suitable to practice the claimed invention. Examiner notes the claims read on all compounds possessing the envisioned physiological activity, disclosed, or undisclosed, regardless the structural formula of these compounds.

- 2) the amount of direction or guidance provided,

In the instant case, only a limited number of "estradiol metabolite" examples are set forth, thereby failing to provide sufficient working examples. Those compounds disclosed in the instant specification encompass only a small number of those compound classes envisioned as possessing physiological activity required to practice

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the invention as herein claimed. Absent that small genus of compounds herein recited, the instant specification is silent as to making, or using, those other compound genera encompassed by the instant claims. Although the specification directs the skilled artisan to specific compounds such as 2-hydroxyestradiol, 2-methoxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol, the application is silent with regard to selection of any additional compounds structurally unrelated to those few compounds listed in the instant specification.

3) the presence, or absence, of working examples,

Applicant fails to set forth the criteria that structurally defines, or identifies, those compounds possessing "little or no estrogen activity". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "estradiol metabolite" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define those structural classes of compounds required to practice the invention as herein claimed, as required by those guidelines set forth in *In re Wands*, supra. Absent exemplification providing guidance as to these compound classes herein envisioned, the instant specification fails to place those compound classes possessing various structural formulas requiring specific pulmonary hypertension treating activity in the skilled artisan's possession, absent undue experimentation.

4) the nature of the invention,

The instant invention reading on all possible estradiol metabolites possessing the pulmonary hypertension treating activity envisioned, disclosed, or undisclosed, set forth a broad inventive scope. Claims herein presented require all compounds, regardless of structural formula, suspected of possessing the instant recited pulmonary hypertension treatment activity to be assayed individually for their suitability in practicing the invention herein recited.

5) the state of the prior art,

The instant claims read on all "estradiol metabolite", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Although various individual compounds possessing the disclosed pulmonary hypertension treating activity are known to those of skill in the art, no information is provided to guide the skilled artisan to those diverse genera of structurally divergent compounds possessing similar physiological activity. Examiner is unaware of any nexus, stated in the art, or herein disclosed, attributing the herein envisioned physiological activity to one, or another, structural formula. Simply stated the skilled artisan must employ experimentation to discover compounds possessing these pulmonary hypertension treating activities required to practice the claimed invention.

6) the relative skill of those in the art

Those individuals skilled in the art possess the required knowledge to perform those assays employed to identify compounds useful for practicing the invention as herein claimed. Applicants' failure to provide adequate guidance as to the envisioned structural formulas employed in the instant claims requires the skilled artisan to

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establish, by individual assay, each compound deemed suitable for use in the instant invention.

7) the predictability of the art,

The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Disease states herein claimed do not flow from a single biochemical lesion, but form a range of physiological activities. Being a syndrome, the instant claimed malady has no succinct etiological underpinnings, thus the recited conditions are not ameliorated by effecting a single biochemical lesion. That the instant malady is not attributable to a single etiology, with the basis of the disease stated diffuse and multifaceted, the skilled artisan must test each compound against the envisioned biochemical lesion to determine the possible use of such compounds in the instant invention.

8) the breadth of the claims.

The instant claims read on all "estradiol metabolite", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Examiner notes the instant claims fail to provide any guidance as to those structural embodiments inherent in those compounds possessing the pulmonary hypertension treating activity herein envisioned. Applicant's claims encompass every, and all, compounds providing the recited pulmonary hypertension treating activity regardless the structural formula of such compounds. Absent guidance with regard to the structural identifies of those compounds possessing the recited pulmonary hypertension treating activity, each compounds must be identified by experimentation in every case.

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Applicants fail to provide information sufficient to identify the structural formulas of those compounds useful to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 7, 11, 15, 19, 23, 27, 31, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "prodrug of estradiol metabolite" recited in the claims renders the claims indefinite because it is not clear what compounds are encompassed by the claims. In other words, it is not clear what compounds are considered as "prodrug of estradiol metabolite".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2001/0056068 ('068) and Parker et al. (Am. J. Physiol. Lung Cell. Mol., 2000;278:L374-L381) in view of Xiao et al. (Hypertension, 2001;37 [part 2]:645-650).

Chwalisz et al. teaches the method of treating pulmonary hypertension (a nitric oxide deficiency disorder) using estradiol, estriol and estrone (See claims 1, 7, 14, and 16). Chwalisz also suggests the use of continuous or prolong release dosage form (See paragraph 0119]. Examiner notes that estradiol is a prodrug of estradiol metabolite.

Parker et al. teaches estradiol as useful in treating pulmonary hypertension and improving pulmonary hemodynamics and vascular remodeling (See the abstract).

Parker et al. also teaches the vasodilatation of estradiol (See page L374, col. 2 – L375,

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col. 1, first paragraph). Furthermore, Parker et al. also discusses the several mechanisms that estradiol may be involved in for the treatment of pulmonary hypertension, in which the protective mechanism of estradiol is believed through the nitric oxide-cGMP cascade (See page L377, col. 2 last paragraph – L379, col. 1, second paragraph).

The primary references do not expressly teach the employment of hydroxyestradiol or methoxyestradiol in treating pulmonary hypertension.

Xiao et al. teaches the metabolites of estradiol, 2-methoxyestradiol and 2-hydroxyestradiol are more potent than their parent compound, estradiol, in enhancing nitric oxide production.


It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed estradiol metabolites, 2-methoxyestradiol and 2-hydroxyestradiol, in a method of treating pulmonary hypertension and its related disorders.

One of ordinary skill in the art would have been motivated to employ the herein claimed estradiol metabolites, 2-methoxyestradiol and 2-hydroxyestradiol, in a method of treating pulmonary hypertension and its related disorders. Employing 2-methoxyestradiol and 2-hydroxyestradiol to enhance the nitric oxide production to treat a nitric oxide deficiency disorder such as pulmonary hypertension would be reasonably expected to be effective. Examiner notes that the resulting mechanism of estradiol metabolites recited are considered as intrinsic properties within the metabolites of estradiol.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


San-ming Hui
Primary Examiner
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